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Implications of random measurement error in studies adjusting for sexual behaviours

EDITOR,—In their recent review of methodological issues in sexual behaviour research, Fenton *et al*[1] provide a comprehensive overview of the major types of sexual behaviour research, the sources of measurement error which may affect such research, and different approaches to measuring various forms of measurement error. We would like to provide an important footnote on the implications of the poor measurement of sexual behaviours for drawing inferences from studies of sexually transmitted infections (STIs) which attempt to adjust for sexual behaviours in their analyses.

The role of systematic measurement errors in study design and analysis, as described by Fenton *et al*, is widely recognised. Given their impact on inferences of association, great care is taken in most studies to avoid these biases. The effects of random measurement error, or non-differential misclassification, on epidemiological inference typically receive less attention. Most researchers realise that non-differential misclassification of exposure and/or outcome measures will lead to an attenuation of the resulting measure of association.

However, the fact that random measurement error in potential confounding variables may wreak havoc on the inferences which are made from study results is seldom acknowledged. The non-differential misclassification of a dichotomous confounding variable may lead to inadequate statistical adjustment (often referred to as residual confounding) and the false appearance of statistical interaction when none is present.[2] When confounders are measured as polytomous or continuous variables (for example, condom use never/sometimes/always or number of sexual partners), random measurement error can bias the adjusted measure of association unpredictably—in some instances making the adjusted measure of association less accurate than the crude.[3 4] These forms of misclassification are generally of greatest concern when the true exposure-disease association is relatively weak compared with the exposure-confounder and outcome-confounder relation,[5] as is the case in most research around STIs. Even small random errors can have major effects on adjusted measures of association, and the unpredictability of the effects of misclassification may be compounded in multivariate analyses.[6]

With this in mind, Fenton *et al*'s review of the difficulties involved in the accurate measurement of sexual behaviour has powerful implications for studies attempting to control for covariates associated with risk for STIs. Studies which attempt to adjust during statistical analysis for numbers and types of sexual partners, frequency of sexual contacts, or condom use practices, are likely to encounter some degree of random measurement error. Although perhaps non-differential with respect to exposure or outcome, this mismeasurement may lead to unpredictable biases and/or mis-specified analyses, and in turn, spurious inferences.

In summary, the inadequate measurement of sexual behaviour requires special consideration in any study attempting to adjust for the confounding role of sexual behaviours in associations involving STIs. We hope that Fenton *et al*'s review of the challenges posed by the collection of sexual behaviour data helps to draw attention to this frequently overlooked methodological aspect of the epidemiology of STIs.

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Is *Mycoplasma hominis* a vaginal pathogen?

EDITOR,—We would like to comment on the study by Arya and colleagues[1] in which they failed to find evidence for *Mycoplasma hominis* being pathogenic in the vagina, or otherwise contributing to bacterial vaginosis (BV). They mentioned the 21 year old review of Taylor-Robinson and McCormack[2] who surmised that *M hominis* might act in symbiosis with other organisms or as a sole pathogen in BV. The latter was referred to as non-specific vaginitis or *Gardnerella* associated vaginitis at that time, the term BV being used from about 1984. Since then, much has been learned about the vaginal microflora in health and disease, but the question of which bacteria, if indeed any, cause BV remains unanswered. The few *M hominis* organisms in the healthy vagina appear to behave as commensals. We challenged[3] the suggestion of Mårdh and colleagues that *M hominis* was associated with a number of genital signs and symptoms after BV had been excluded, our assertion being that *M hominis* organisms outside the context of BV would be present in small numbers and, therefore, unlikely to cause a problem. In contrast, the few *M hominis* organisms in the healthy vagina increase in number, perhaps by 10 000-fold or more, in the vagina of women with BV. This increase, however, occurs only late in the development of BV.[4] Indeed, it is rare to find large numbers in the "intermediate" (grade 2) stage between the normal vaginal flora and "full blown" BV (grade 3). Thus, in the study by Arya and colleagues we have difficulty in understanding why only 35 (48%) of the 73 women with *M hominis* positive BV had large numbers of organisms ($>5 \times 10^5$). A Gram stain evaluation should have distinguished women with grade 2 flora from those with grade 3. Be this as it may, the authors contend that because the additional presence of *M hominis* with *G vaginalis* and strict anaerobes did not seem to increase the likelihood of the women developing BV, *M hominis* is not involved. It is clear that *M hominis* organisms are not essential for the development of BV and unlikely that their initial presence in the vagina increases the likelihood of BV developing. However, if they are present in the vagina initially, then they will multiply as indicated and large numbers will ensue. The data of Arya and colleagues do not resolve the issue of whether large numbers contribute to the disease process or are involved in its persistence. Against this, as they point out, is a study[5] in which metronidazole, inactive in vitro against *M hominis*, cleared vaginitis, and doxycycline, active against *M hominis*, did not. However, it should also be remembered that *M hominis* organisms caused pharyngitis and cervical lymphadenopathy when given orally in large numbers to volunteers,[6] indicating the pathogenic potential of the organisms. Furthermore, the *M hominis* species is heterogeneous, some strains having greater epithelial cell adherence properties than others. We do not see any data that point to *M hominis* being a sole pathogen or co-pathogen in the vagina but, equally, we are not convinced by data that purport to show that it is not.

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Response of hepatitis B induced membranoproliferative glomerulonephritis to HAART

EDITOR,—Renal disease occurring in HIV infected individuals is well described.[1 2] HIV associated nephropathy (HIVAN) is the

predominant renal lesion in black patients, whereas immune complex and membranous nephropathy occur more commonly in white patients.[1] Improvements in renal function have been described with highly active antiretroviral therapy (HAART) when the underlying renal lesion is HIVAN or membranous nephropathy.[3–5] We report here an HIV infected patient in whom renal disease caused by hepatitis B induced membranoproliferative glomerulonephritis improved with HAART.

A 34 year old white homosexual man was found to be HIV-1 antibody positive in August 2000 after he presented with biopsy proved Kaposi's sarcoma. At this time he also reported 2 months of fatigue and frothy urine. In the past he had been found to be hepatitis BeAg positive in 1996. Examination revealed multiple cutaneous Kaposi's sarcoma, BP = 170/100, no peripheral oedema, and scanty retinal haemorrhages on funduscopy. Investigations showed blood urea = 9.2 (normal = 2.8–7.6) mmol/l, serum creatinine = 178 (normal = 80–133) µmol/l, normal serum, potassium, and sodium. Liver function tests were normal apart from a serum albumin of 29 (normal = 35–50) g/l. The haemoglobin was 9.3 g/dl and white blood cell and platelet counts were normal. The CD4 count was 110 cells $\times 10^6$/l and HIV viral load was 47 500 copies/ml. Complement C3 was 0.56 (normal = 0.9–1.8) g/l, C4 was 0.07 (normal = 0.1—0.4) g/l. Immunoglobulin quantification showed normal IgA, IgG = 23.2 (normal = 7.0—16.0) mg/l and IgM = 4.4 (normal = 0.4—2.3) g/l. Hepatitis B serology showed HbeAg+ and HbsAg+ (titre 1:3200). Urinalysis showed blood +++ and ++++ protein. Urine protein = 5.8 g/24 hours and creatinine clearance = 66 ml/min. Ultrasound examination showed normal sized kidneys. Histology of a renal biopsy showed membranoproliferative glomerulonephritis. Staining showed marked deposits of hepatitis B core and surface antigens (fig 1).

The patient was managed conservatively. HAART was commenced with efavirenz, didanosine, and stavudine and hypertension was treated with ramipril. After 8 weeks of HAART the CD4 count was 140 cells $\times 10^6$/l and viral load was 100 copies/ml. The serum creatinine returned to normal and there was no persistent proteinuria.

This case illustrates the importance of considering non-HIV associated pathology in the HIV infected patient presenting with renal disease. It also shows the value of renal biopsy in identifying the precise cause of the presentation. This patient demonstrates that non-HIV hepatitis B associated renal disease may improve with HAART. The exact mechanism for this remains unclear.

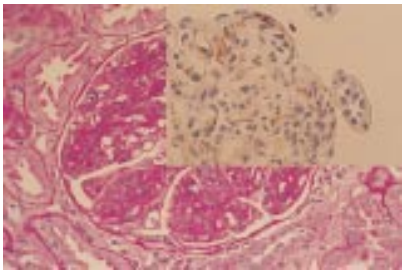

Figure 1 Renal histology shows glomerular mesangial expansion and thickening of the capillary walls, characteristic of membranoproliferative glomerulonephritis. The mesangial areas and capillary walls were positive for IgG, IgA, IgM, and complement components C3 and C1q. There was also positive staining for hepatitis B surface and core (inset) antigens. Haematoxylin and eosin ×400 and immunoperoxidase ×400 (inset).

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Cervical cytology smears in sexually transmitted infection clinics in the United Kingdom

EDITOR,—I found the article by Janet Wilson and Wendy Parsons on behalf of the BCCG, concerning cervical cytology practice in UK genitourinary medicine clinics, comprehensive and reassuring in terms of our practice.[1]

The final statement "there is therefore no evidence from this study to support the practice of additional smears in the presence of an effective national cytology screening programme" is both justified and a case well made.

The paper calls additional smears "opportunistic" and recognises them as being performed in women less than the age of 20, women with genital warts, and in some who have had a normal smear within the previous 3 years.

The *OED* definition of opportunity is "favourable, appropriate or advantageous combination of circumstances."[2] There is no evidence to suggest that offering smears in these circumstances fulfils this description. If this is so, then we are depriving women such as teenagers of a valuable health screen and patently this is not the case.

I would like to propose, therefore, that we no longer continue to call these smears "opportunistic" but use the term "unnecessary."

The recognition of this could be an advance for evidence based practice, help to reduce unnecessary anxiety, and release much needed resources.

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BOOK REVIEW

The Wages of Sin. Sex and Disease, Past and Present. By P L Allen. £17.50; pp 202. Chicago: University of Chicago Press, 2000. ISBN 0 226 01460 6.

This is a profound work describing the impact of venereal diseases and conventional morality in the build up to AIDS. It is written by an American, who has been personally affected by the impact of AIDS. He has written a book on topics in history relating to sex, morality, and infectious diseases, which have had an impact on the public response to AIDS. Throughout, one senses the author's very real loss in what to him and many others have been tragic times.

It is interesting to see how different the general public moral climate is in different societies in the developed world. Thankfully, some forms of evangelism do not have the same influence everywhere.

Does the historical part of the book tell the medical historian anything new? The answer is yes. And that is the gap between what has been known on this subject to academics for a long time and what others are only finding out about now. The chapters containing information on the church's attitude to sexual morality; on leprosy, the early history of syphilis, bubonic plague, and masturbation illustrate the age old story of reactionary view against progress. It is difficult to judge the mores of the past through the views of the present.

It is a pity that the author seems to have given such prominence to those whose views resisted progress. Nothing is mentioned of liberal pioneers in venereal diseases from Van Swieten in the 18th century, through Ricord, Fournier in the next, Abraham Flexner (for the Rockerfeller Foundation), Neisser, or indeed the enormous changes brought about by the Royal Commission on Venereal Diseases in Great Britain at the time of the first world war or such notable more recent Americans such as Kampmeier, Stokes, or Earl Moore.

The chapters on America are particularly interesting from a European point of view. Learning about reactionary views always helps in developing any strategy for public knowledge and education. Well educated AIDS lobbyists have certainly had an impact in Europe as in the United States and are neatly described in this work. The bibliography, 14 pages, is particularly good.

This is a book questioning responses and conventional morality in respect, sorrow, and anguish. It is worthy of merit. It enables the modern reader to learn about difficult aspects of morality in relation to venereal diseases and sexuality which have always had more impact on the public than the practising physician.

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